Amendments to the Specification:

Please replace paragraph **[06]** beginning at page 2, line 6, with the following:

--**[06]** The ADNF I polypeptides have an active core site comprising the following amino acid sequence: Ser-Ala-Leu-Leu-Arg-Ser-Ile-Pro-Ala ("SALLRSIPA" (SEQ ID NO:1) or in short referred to as "SAL" or "ADNF-9"). The ADNF III polypeptides also have an active core site comprising a few amino acid residues, namely, the following amino acid sequence: Asn-Ala-Pro-Val-Ser-Ile-Pro-Gln ("NAPVSIPQ" (SEQ ID NO:2) or in short referred as "NAP"). These ADNF polypeptides have previously been shown, each on their own, to have remarkable potency and activity in animal models related to neurodegeneration.--

Please replace paragraph **[07]** beginning at page 2, line 13, with the following:

--**[07]** In one embodiment, the method comprises administering an ADNF polypeptide, wherein the ADNF polypeptide is an ADNF I polypeptide comprising an active core site having the amino acid sequence of Ser-Ala-Leu-Leu-Arg-Ser-Ile-Pro-Ala (SEQ ID NO:1). In another embodiment, the method comprises administering a full length ADNF I polypeptide. In yet another embodiment, the method comprises administering an ADNF I polypeptide which consists of the amino acid sequence of Ser-Ala-Leu-Leu-Arg-Ser-Ile-Pro-Ala (SEQ ID NO:1). In yet another embodiment, the method comprises administering an ADNF I polypeptide, wherein the ADNF I polypeptide is selected from the group consisting of: Val-Leu-Gly-Gly-Gly-Ser-Ala-Leu-Leu-Arg-Ser-Ile-Pro-Ala ~~(SEQ ID NO:14)~~ (SEQ ID NO:3); Val-Glu-Glu-Gly-Ile-Val-Leu-Gly-Gly-Gly-Ser-Ala-Leu-Leu-Arg-Ser-Ile-Pro-Ala ~~(SEQ ID NO:15)~~ (SEQ ID NO:4); Leu-Gly-Gly-Gly-Ser-Ala-Leu-Leu-Arg-Ser-Ile-Pro-Ala ~~(SEQ ID NO:16)~~ (SEQ ID NO:5); Gly-Gly-Gly-Ser-Ala-Leu-Leu-Arg-Ser-Ile-Pro-Ala ~~(SEQ ID NO:17)~~ (SEQ ID NO:6); Gly-Gly-Ser-Ala-Leu-Leu-Arg-Ser-Ile-Pro-Ala ~~(SEQ ID NO:18)~~ (SEQ ID NO:7); and Gly-Ser-Ala-Leu-Leu-Arg-Ser-Ile-Pro-Ala ~~(SEQ ID NO:19)~~ (SEQ ID NO:8). In yet another

embodiment, the method comprises administering an ADNF I polypeptide having up to about 20 amino acids at at least one of the N-terminus or the C-terminus of the active core site. In certain embodiments, the ADNF I polypeptide has up to 20 amino acids at both the N-terminus and the C-terminus of the ADNF I polypeptide.--

Please replace paragraph **[08]** beginning at page 2, line 30, with the following:

--**[08]** In some embodiments, the method comprises administering an ADNF III polypeptide, wherein the ADNF polypeptide is a polypeptide comprising an active core site having the amino acid sequence of Asn-Ala-Pro-Val-Ser-Ile-Pro-Gln ~~(SEQ ID NO:1)~~ (SEQ ID NO:2). In yet another embodiment, the method comprises administering a full length ADNF III polypeptide. In yet another embodiment, the method comprises administering an ADNF I polypeptide which consists of the amino acid sequence of Asn-Ala-Pro-Val-Ser-Ile-Pro-Gln ~~(SEQ ID NO:1)~~ (SEQ ID NO:2). In yet another embodiment, the method comprises administering an ADNF III polypeptide, wherein the ADNF III polypeptide is selected from the group consisting of: Gly-Gly-Asn-Ala-Pro-Val-Ser-Ile-Pro-Gln ~~(SEQ ID NO:2)~~ (SEQ ID NO:9); Leu-Gly-Gly-Asn-Ala-Pro-Val-Ser-Ile-Pro-Gln-Gln-Ser ~~(SEQ ID NO:3)~~ (SEQ ID NO:10); Leu-Gly-Leu-Gly-Gly-Asn-Ala-Pro-Val-Ser-Ile-Pro-Gln-Gln-Ser ~~(SEQ ID NO:4)~~ (SEQ ID NO:11); and Ser-Val-Arg-Leu-Gly-Leu-Gly-Gly-Asn-Ala-Pro-Val-Ser-Ile-Pro-Gln-Gln-Ser ~~(SEQ ID NO:5)~~ (SEQ ID NO:12). In yet another embodiment, the method comprises administering an ADNF polypeptide having up to about 20 amino acids at at least one of the N-terminus and the C-terminus of the active core site. In certain embodiments, the ADNF polypeptide has up to 20 amino acids at both the N-terminus and the C-terminus of the ADNF polypeptide.--

Please replace paragraph **[16]** beginning at page 4, line 6, with the following:

--**[16]** The phrase "ADNF polypeptide" refers to one or more activity dependent neurotrophic factors (ADNF) that have an active core site comprising the amino acid sequence of

SALLRSIPA (SEQ ID NO:1) (referred to as "SAL") or NAPVSIPQ (SEQ ID NO:2) (referred to as "NAP"), or conservatively modified variants thereof that have neurotrophic/neuroprotective activity as measured with *in vitro* cortical neuron culture assays described by, e.g., Hill *et al.*, *Brain Res.* 603, 222-233 (1993); Brenneman *et al.*, *Nature* 335, 636 (1988); Brenneman *et al.*, *Dev. Brain Res.* 51:63 (1990); Forsythe & Westbrook, *J. Physiol. Lond.* 396:515 (1988); Gozes *et al.*, *Proc. Natl. Acad. Sci. USA* 93: 427 (1996). An ADNF polypeptide can be an ADNF I polypeptide, an ADNF III polypeptide, their alleles, polymorphic variants, analogs, interspecies homolog, any subsequences thereof (e.g., SALLRSIPA (SEQ ID NO:1) or NAPVSIPQ (SEQ ID NO:2)) or lipophilic variants that exhibit neuroprotective/neurotrophic action on, e.g., neurons originating in the central nervous system either *in vitro* or *in vivo*. An "ADNF polypeptide" can also refer to a mixture of an ADNF I polypeptide and an ADNF III polypeptide.--

Please replace paragraph **[17]** beginning at page 4, line 19, with the following:

--**[17]** The term "ADNF I" refers to an activity dependent neurotrophic factor polypeptide having a molecular weight of about 14,000 Daltons with a pI of 8.3 ± 0.25. As described above, ADNF I polypeptides have an active site comprising an amino acid sequence of Ser-Ala-Leu-Leu-Arg-Ser-Ile-Pro-Ala (also referred to as "SALLRSIPA" (SEQ ID NO:1) or "SAL" or "ADNF-9"). *See*, Brenneman & Gozes, *J. Clin. Invest.* 97:2299-2307 (1996); Glazner *et al.*, *Anat. Embryol.* 200: 65 (1999); Brenneman *et al.*, *J. Pharm. Exp. Ther.*, 285:619-27 (1998); Gozes & Brenneman, *J. Mol. Neurosci.* 7:235-244 (1996); Gozes *et al.*, *Dev. Brain Res.* 99:167-175 (1997); and Gozes *Trends in Neurosci.* 24: 700 (2001), all of which are herein incorporated by reference. Unless indicated as otherwise, "SAL" refers to a peptide having an amino acid sequence of Ser-Ala-Leu-Leu-Arg-Ser-Ile-Pro-Ala (SEQ ID NO:1), not a peptide having an amino acid sequence of Ser-Ala-Leu. A full length amino acid sequence of ADNF I can be found in WO 96/11948, herein incorporated by reference in its entirety.--

Please replace paragraph **[18]** beginning at page 4, line 31, with the following:

--**[18]** The phrase "ADNF III polypeptide" or "ADNF III" refers to one or more activity dependent neurotrophic factors (ADNF) that have an active core site comprising the amino acid sequence of NAPVSIPQ (SEQ ID NO:2) (referred to as "NAP"), or conservatively modified variants thereof that have neurotrophic/neuroprotective activity as measured with *in vitro* cortical neuron culture assays described by, e.g., Hill *et al.*, *Brain Res.* 603, 222-233 (1993); Gozes *et al.*, *Proc. Natl. Acad. Sci. USA* 93, 427-432 (1996). An ADNF polypeptide can be an ADNF III polypeptide, allelelic or polymorphic variant, analog, interspecies homolog, or any subsequences thereof (e.g., NAPVSIPQ; SEQ ID NO:2) that exhibit neuroprotective/neurotrophic action on, e.g., neurons originating in the central nervous system either *in vitro* or *in vivo*. ADNF III polypeptides can range from about eight amino acids and can have, e.g., between 8-20, 8-50, 10-100 or about 1000 or more amino acids.--

Please replace paragraph **[19]** beginning at page 5, line 8, with the following:

--**[19]** Full length human ADNF III has a predicted molecular weight of 123,562.8 Da (>1000 amino acid residues) and a pI of about 6.97. As described above, ADNF III polypeptides have an active site comprising an amino acid sequence of Asn-Ala-Pro-Val-Ser-Ile-Pro-Gln (also referred to as "NAPVSIPQ" (SEQ ID NO:2) or "NAP"). *See*, Zamostiano *et al.*, *J. Biol. Chem.* 276:708-714 (2001) and Bassan *et al.*, *J. Neurochem.* 72:1283-1293 (1999), each of which is incorporated herein by reference. Unless indicated as otherwise, "NAP" refers to a peptide having an amino acid sequence of Asn-Ala-Pro-Val-Ser-Ile-Pro-Gln (SEQ ID NO:2), not a peptide having an amino acid sequence of Asn-Ala-Pro. Full-length sequences of ADNF III can be found in WO 98/35042 and WO 00/27875.--

Please replace paragraph **[45]** beginning at page 12, line 31, with the following:

--**[45]** In one aspect, the method comprises administering an ADNF I polypeptide that comprises an active core site having the following amino acid sequence: Ser-Ala-Leu-Leu-Arg-Ser-Ile-Pro-Ala (SEQ ID NO:1). In one embodiment, the ADNF I polypeptide consists of an active core site that has an amino acid sequence of Ser-Ala-Leu-Leu-Arg-Ser-Ile-Pro-Ala (SEQ ID NO:1). In another embodiment, the ADNF I polypeptide can comprise additional amino acids at the N-terminus and/or at the C-terminus of the active core site. For example, the ADNF I polypeptide can comprise up to 40 amino acids at the N-terminus and/or the C-terminus of the active core site. In another example, the ADNF I polypeptide can comprise up to 20 amino acids at the N-terminus and/or the C-terminus of the active core site. In yet another example, the ADNF I polypeptide can comprise up to 10 amino acids at the N-terminus and/or the C-terminus of the active core site. In yet another embodiment, the ADNF I polypeptide can be a full length ADNF I polypeptide.--

Please replace paragraph **[46]** beginning at page 13, line 9, with the following:

--**[46]** In another aspect, the method comprises administering to the subject an ADNF III polypeptide that comprises an active core site having the following amino acid sequence: Asn-Ala-Pro-Val-Ser-Ile-Pro-Gln (SEQ ID NO:2). In one embodiment, the ADNF III polypeptide consists of an active core site that has an amino acid sequence of Asn-Ala-Pro-Val-Ser-Ile-Pro-Gln (SEQ ID NO:2). In another embodiment, the ADNF III polypeptide can comprise additional amino acids at the N-terminus and/or at the C-terminus of the active core site. For example, the ADNF III polypeptide can comprise up to 40 amino acids at the N-terminus and/or the C-terminus of the active core site. In another example, the ADNF III polypeptide can comprise up to 20 amino acids at the N-terminus and/or the C-terminus of the active core site. In yet another example, the ADNF III polypeptide can comprise up to 10 amino

acids at the N-terminus and/or the C-terminus of the active core site. In yet another embodiment, the ADNF III polypeptide can be a full length ADNF III polypeptide.--

Please replace paragraph **[47]** beginning at page 13, line 21, with the following:

--**[47]** In a preferred embodiment, the ADNF I polypeptide comprises an amino acid sequence of $(R^1)_x$-Ser-Ala-Leu-Leu-Arg-Ser-Ile-Pro-Ala-$(R^2)_y$ (SEQ ID NO:13), and the ADNF III polypeptide comprises an amino acid sequence of $(R^3)_w$-Asn-Ala-Pro-Val-Ser-Ile-Pro-Gln-$(R^4)_z$ (SEQ ID NO:14).--

Please replace paragraph **[49]** beginning at page 14, line 1, with the following:

--**[49]** Within the above formula for the ADNF I polypeptide, x and y are independently selected and are equal to zero or one. The term independently selected is used herein to indicate that x and y may be identical or different. For example, x and y may both be zero or, alternatively, x and y may both be one. In addition, x may be zero and y may be one or, alternatively, x may be one and y may be zero. Moreover, if x and y are both one, the amino acid sequences R^1 and R^2 may be the same or different. As such, the amino acid sequences R^1 and R^2 are independently selected. If R^1 and R^2 are the same, they are identical in terms of both chain length and amino acid composition. For example, both R^1 and R^2 may be Val-Leu-Gly-Gly-Gly (SEQ ID NO:15). If R^1 and R^2 are different, they can differ from one another in terms of chain length and/or amino acid composition and/or order of amino acids in the amino acids sequences. For example, R^1 may be Val-Leu-Gly-Gly-Gly (SEQ ID NO:15), whereas R^2 may be Val-Leu-Gly-Gly (SEQ ID NO:16). Alternatively, R^1 may be Val-Leu-Gly-Gly-Gly (SEQ ID NO:15), whereas R^2 may be Val-Leu-Gly-Gly-Val (SEQ ID NO:17). Alternatively, R^1 may be Val-Leu-Gly-Gly-Gly (SEQ ID NO:15), whereas R^2 may be Gly-Val-Leu-Gly-Gly (SEQ ID NO:18).--

Please replace paragraph **[50]** beginning at page 14, line 15, with the following:

--**[50]** Similarly, w and z are independently selected and are equal to zero or one within the above formula for the ADNF III polypeptide. The term independently selected is used herein to indicate that w and z may be identical or different. For example, w and z may both be zero or, alternatively, w and z may both be one. In addition, w may be zero and z may be one or, alternatively, w may be one and z may be zero. Moreover, if w and z are both one, the amino acid sequences R^3 and R^4 may be the same or different. As such, the amino acid sequences R^3 and R^4 are independently selected. If R^3 and R^4 are the same, they are identical in terms of both chain length and amino acid composition. For example, both R^3 and R^4 may be Leu-Gly-Leu-Gly-Gly (SEQ ID NO:19). If R^3 and R^4 are different, they can differ from one another in terms of chain length and/or amino acid composition and/or order of amino acids in the amino acids sequences. For example, R^3 may be Leu-Gly-Leu-Gly-Gly (SEQ ID NO:19), whereas R^4 may be Leu-Gly-Leu-Gly (SEQ ID NO:20). Alternatively, R^3 may be Leu-Gly-Leu-Gly-Gly (SEQ ID NO:19), whereas R^4 may be Leu-Gly-Leu-Gly-Leu (SEQ ID NO:21).--

Please replace paragraph **[51]** beginning at page 14, line 28, with the following:

--**[51]** Within the scope, certain ADNF I and ADNF III polypeptides are preferred, namely those in which x, y, w, and z are all zero (*i.e.*, SALLRSIPA (SEQ ID NO:1) and NAPVSIPQ (SEQ ID NO:1), respectively). Equally preferred are ADNF I polypeptides in which x is one; R^1 is Val-Leu-Gly-Gly-Gly (SEQ ID NO:15); and y is zero. Also equally preferred are ADNF I polypeptides in which x is one; R^1 is Val-Glu-Glu-Gly-Ile-Val-Leu-Gly-Gly-Gly (SEQ ID NO:22); and y is zero. Also equally preferred are ADNF III polypeptides in which w is one; R^3 is Gly-Gly; and z is zero. Also equally preferred are ADNF III polypeptides in which w is one; R^3 is Leu-Gly-Gly; z is one; and R^4 is Gln-Ser. Also equally preferred are ADNF III polypeptides in which w is one; R^3 is Leu-Gly-Leu-Gly-Gly- (SEQ ID NO:19); z is one; and R^4 is Gln-Ser. Also equally preferred are ADNF III polypeptides in which w is one; R^3

is Ser-Val-Arg-Leu-Gly-Leu-Gly-Gly (SEQ ID NO:23); z is one; and R^4 is Gln-Ser. Additional amino acids can be added to both the N-terminus and the C-terminus of these active sites (SALLRSIPA (SEQ ID NO:1) or NAPVSIPQ (SEQ ID NO:2)) without loss of biological activity as evidenced by the fact that the intact ADNF I or ADNF III growth factors exhibit extraordinary biological activity. *See*, U.S.S.N. 08/324,297, filed October 17, 1994 (also published as WO96/11948) for the description of ADNF I polypeptides; and U.S.S.N. 60/037,404 filed February 27, 1997 and U.S.S.N. 60/059,621 filed, September 23, 1997 (also published as WO98/35042) for the description of ADNF III polypeptides, all of which are incorporated herein by reference.--

Please replace paragraph **[60]** beginning at page 17, line 30, with the following:

--**[60]** Small polypeptides including SALLRSIPA (SEQ ID NO:1) and NAPVSIPQ (SEQ ID NO:2) cross the blood brain barrier. For longer polypeptides that do not the cross blood brain barrier, methods of administering proteins to the brain are well known. For example, proteins, polypeptides, other compounds and cells can be delivered to the mammalian brain via intracerebroventricular (ICV) injection or via a cannula (*see, e.g.*, Motta & Martini, *Proc. Soc. Exp. Biol. Med.* 168:62-64 (1981); Peterson *et al., Biochem. Pharamacol.* 31:2807-2810 (1982); Rzepczynski *et al., Metab. Brain Dis.* 3:211-216 (1988); Leibowitz *et al., Brain Res. Bull.* 21:905-912 (1988); Sramka *et al., Stereotact. Funct. Neurosurg.* 58:79-83 (1992); Peng *et al., Brain Res.* 632:57-67 (1993); Chem *et al., Exp. Neurol.* 125:72-81 (1994); Nikkhah *et al., Neuroscience* 63:57-72 (1994); Anderson *et al., J. Comp. Neurol.* 357:296-317 (1995); and Brecknell & Fawcett, *Exp. Neurol.* 138:338-344 (1996)). In particular, cannulas can be used to administer neurotrophic factors to mammals (*see, e.g.*, Motta & Martini, *Proc. Soc. Exp. Biol. Med.* 168:62-64 (1981) (neurotensin); Peng *et al., Brain Res.* 632:57-67 (1993) (NGF); Anderson *et al., J. Comp. Neurol.* 357:296-317 (1995) (BDNF, NGF, neurotrophin-3).--

Please replace paragraph **[96]** beginning at page 29, line 3, with the following:

--**[96]** One of skill will recognize many ways of generating alterations in a given nucleic acid sequence. Such well-known methods include site-directed mutagenesis, PCR amplification using degenerate oligonucleotides, exposure of cells containing the nucleic acid to mutagenic agents or radiation, chemical synthesis of a desired oligonucleotide (e.g., in conjunction with ligation and/or cloning to generate large nucleic acids) and other well-known techniques (*see* Giliman & Smith, *Gene* 8:81-97 (1979); Roberts *et al.*, *Nature* 328:731-734 (1987)). For example, alanine scanning can be used to determine conservatively modified variants for NAPVSIPQ (SEQ ID NO:2) (*i.e.*, by substituting each amino acid one by one with an alanine or other small neutral amino acid and assay for activity as described herein).--

Please replace paragraph **[99]** beginning at page 29, line 20, with the following:

--**[99]** Using these assays, one of ordinary skill in the art can readily prepare a large number of ADNF polypeptides in accordance with the teachings of the present invention and, in turn, screen them using the foregoing assay to find ADNF III polypeptides, in addition to those set forth herein, which possess the neuroprotective/neurotrophic activity of the intact ADNF III growth factor. For instance, using ADNF III-8 (*i.e.*, Asn-Ala-Pro-Val-Ser-Ile-Pro-Gln; SEQ ID NO:2) as a starting point, one can systematically add, for example, Gly-, Gly-Gly-, Leu-Gly-Gly- to the N-terminus of ADNF III-8 and, in turn, screen each of these ADNF III polypeptides in the foregoing assay to determine whether they possess neuroprotective/ neurotrophic activity. In doing so, it will be found that additional amino acids can be added to both the N-terminus and the C-terminus of the newly discovered active site, *i.e.*, Asn-Ala-Pro-Val-Ser-Ile-Pro-Gln (SEQ ID NO:2), without loss of biological activity as evidenced by the fact that the intact ADNF III growth factor exhibits extraordinary biological activity. This discussion also applies to ADNF I polypeptides.--

Please replace paragraph **[102]** beginning at page 30, line 14, with the following:

--**[102]** The present study demonstrates that administration of the NAP (Asn-Ala-Pro-Val-Ser-Ile-Pro-Gln, single-letter code: NAPVSIPQ (SEQ ID NO:2)) peptide decreases disease indications in MOG-induced EAE mice.--

Please insert the accompanying paper copy of the Sequence Listing, page numbers 1 to 7, at the end of the application.